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# The impact of biomarkers in early detection of acute mesenteric ischemia

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**ADMINISTRATIVE INFORMATION**

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**Conflicts of interest -** None declared.

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**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 December 2023 and was last updated on 21 December 2023.

## INTRODUCTION

**Review question / Objective** This study's objective is to systematically review existing literature to extract crucial insights regarding potential biomarkers for the early detection of acute mesenteric ischemia in the human population.

**Rationale** Acute mesenteric ischemia (AMI) is a life-threatening condition characterized by inadequate blood flow in the mesenteric vessels, leading to ischemia and eventual necrosis of the intestines. AMI encompasses four different clinical entities with different etiologies: acute mesenteric arterial embolism (AMAE), acute mesenteric arterial thrombosis. (AMAT), non-occlusive mesenteric ischemia (NOMI), and mesenteric venous thrombosis (MVT). The incidence of AMI is relatively low, estimated at around 0.2% of all acute surgical admissions, but its mortality rate ranges from 50% to 80%. Early and reliable detection, in addition to appropriate emergency tools, can limit the long-term consequences of AMI, which is important in terms of quality of survival and reducing the incidence of mortality. Studies have demonstrated that intestinal ischemia occurs when the blood supply is reduced by more than 50% or the patient's mean arterial pressure drops below 45 mmHg. Although the small intestine has the ability to compensate for a reduction of up to 3⁄4 in blood supply for approximately 12 hours. AMI is caused by various types of pathology and its underlying factors. Conditions that lead to arterial embolism, including valvular heart disease, atrial fibrillation or flutter, myocardial infarction, cardiac valvular vegetation, mechanical valve prostheses and cardiomyopathies lead to AMAE. AMAT can be caused by atherosclerotic disease, congestive

heart failure, vasculitis, conditions that lead to low cardiac output, procoagulative status and iatrogenic causes (cardiac catheterization related emboli and angiography). NOMI may result from some form of shock, as can occur with heart failure or poor controlled vasopressors, or because of excessive diuretic-associated volume depletion. On the other hand, MVT is mostly caused by conditions that lead to a hypercoagulable state, intra-abdominal infections, portal hypertension, increased intra-abdominal pressure and venous trauma. The extent of ischemic injury in the intestinal mucosa is largely reversible, except when transmural injury occurs, leading to inflammation, necrosis, sepsis, and multiple organ failure (MOF). Symptoms of AMI are often nonspecific and include moderate to severe diffuse pain, nausea, vomiting, and diarrhea progressing to obstipation, abdominal distention, and gastrointestinal bleeding. With the progression of intestinal necrosis, signs of sepsis such as tachycardia, tachypnea, hypotension, fever, and altered mental status may develop. According to the current guidelines, computed tomography angiogram (CTA) is recognized as the most efficacious diagnostic tool for detecting AMI, with a sensitivity of 85–98% and specificity of 91–100%. Plain abdominal radiography's diagnostic usefulness in AMI is restricted, as it only becomes positive only in cases of perforation leading to the presence of free air beneath the diaphragm. While definitive and accurate biomarkers have not been pinpointed, laboratory findings can help corroborate clinical suspicions. Potential markers like serum lactate levels, D-dimer, amylase, I-FABP, and alpha-GST could augment diagnostic precision. Biomarkers have gained prominence in diverse clinical domains, assisting in disease prediction and monitoring. They offer significant advantages to both clinicians and patients by diminishing the necessity for invasive and time-consuming procedures. Furthermore, these markers can be conveniently measured in blood and urine samples.

**Condition being studied** Acute mesenteric ischemia (AMI) is a life-threatening condition characterized by inadequate blood flow in the mesenteric vessels, leading to ischemia and eventual necrosis of the intestines. AMI encompasses four different clinical entities with different etiologies: acute mesenteric arterial embolism (AMAE), acute mesenteric arterial thrombosis (AMAT), non-occlusive mesenteric ischemia (NOMI), and mesenteric venous thrombosis (MVT). The incidence of AMI is relatively low, estimated at around 0.2% of all acute surgical admissions, but its mortality rate ranges from 50% to 80%. Early and reliable detection, in addition to appropriate emergency tools, can limit the long-term consequences of AMI, which is important in terms of quality of survival and reducing the incidence of mortality.

## METHODS

**Search strategy** The searched terms utilized were as follows: (exp mesenteric ischemia/ OR exp intestine ischemia/ OR exp mesenteric ischemia/ OR acute mesenteric ischemia.mp.) AND (exp marker/ OR exp biological marker/ OR exp biochemical marker/ OR exp molecular marker/ OR exp disease marker/ OR exp tumor marker/ OR exp cell marker/ OR cell surface marker/ OR exp biopsy site marker/ OR cell membrane marker/) AND (exp laboratory diagnosis/ OR exp diagnosis/ OR exp early diagnosis/).

**Participant or population** Adult patients diagnosed with acute mesenteric ischemia, intestinal ischemia, small bowel obstruction, bowel necrosis, reversible/irreversible bowel ischemia, a mesenteric infarction.

**Intervention** NA.

**Comparator** NA.

**Study designs to be included** Randomized controlled studies, Cohort Studies on human population.

**Eligibility criteria** Adult patients diagnosed with acute mesenteric ischemia, intestinal ischemia, small bowel obstruction, bowel necrosis, reversible/irreversible bowel ischemia, a mesenteric infarction; English, Slovenian, Serbo-Croatian, Macedonian language; Freely available studies.

**Information sources** PubMed, Embase, Medline, Cochrane library databases and Cross-referencing.

**Main outcome(s)** This systematic review aimed to gather available information on potential biomarkers for diagnosing AMI. From a total of 654 articles, 46 articles examining 14 different biomarkers were filtered, falling within our inclusion criteria. Intestinal fatty acid-binding protein (IFABP) was the most commonly researched biomarker regarding AMI with sensitivity ranging from 61.5% to 100% and specificity ranging from 40% to 100%. The second most commonly researched biomarker was D-dimer with sensitivity of 60-100% and specificity of 18-85.71%. L-lactate had a sensitivity of 36.6-90.91% and specificity of

64.29-96%. Several parameters within the blood count were examined as potential markers for AMI including: NLR, PLR, MPV, RDW, DNI and IG. Citrulline, interleukin 6 (IL-6), and procalcitonin (PCT) were the least researched biomarkers.

**Quality assessment / Risk of bias analysis** Small sample sizes, observed in some of the included studies, could lead to an overestimation of the true diagnostic accuracy of biomarkers for acute intestinal ischemia. Additionally, different studies employ varying cutoff values, ranging from picometers to nanometers, making it challenging to determine the optimal cutoff value. The use of different screening methods for the same markers further complicates the standardization of identifying the most effective marker. Moreover, the reference tests for diagnosing AMI differ across studies. While histopathological examination serves as the golden standard reference, its complexity in acquiring pathological specimens for certain diseases is often overlooked. Some included studies relied on radiological examination or mixed reference standards to diagnose acute intestinal ischemia, potentially resulting in an overestimation of diagnostic accuracy. Furthermore, many less-known biomarkers have predominantly been studied on animal subjects, leading to a limited number of studies available for sensible comparison with our systematic review. A common challenge in systematic reviews is the presence of language barriers that may result in excluding publications that do not meet the inclusion criteria. In our study, due to limited resources and team capacity, we only included studies published in English, Slovenian, Serbo-Croatian, or Macedonian, which could introduce language bias. Furthermore, the bibliography exclusively comprises freely available articles.

**Strategy of data synthesis** Following the completion of the search, duplicate articles were removed. In the initial selection phase, two authors assessed the titles and abstracts of all identified articles based on predefined eligibility criteria. In the subsequent selection phase, full-text articles were thoroughly examined to determine their eligibility for further inclusion. Additionally, the references of relevant reviews were screened to identify any additional articles that met the inclusion criteria. In the event of any difference in opinion regarding the inclusion of an article, the authors engaged in discussions to reach a final decision.

**Subgroup analysis** The relationship between different biomarkers and their sensitivity and specificity in early recognition of AMI.

**Sensitivity analysis** Not reported.

**Language restriction** English, Slovenian, Macedonian, Serbo-Croatian.

**Country(ies) involved** Slovenia.

**Keywords** Biomarkers; acute mesenteric ischemia; early diagnosis.

**Contributions of each author**

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